Rifampicin-induced Renal Toxicity During Retreatment of Patients with Pulmonary Tuberculosis

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Abstract
Rifampicin is a crucial component of treatment regimens for tuberculosis and has been in use since the early 1970’s. It is usually considered safe. Rarely life-threatening complications like acute renal failure or acute thrombocytopenia may manifest during treatment with rifampicin. In our experience at the Tuberculosis Research Centre of treating more than 8000 pulmonary and extrapulmonary tuberculosis patients with rifampicin-containing regimens over the last 30 years, we are reporting 3 cases of probably rifampicin-induced acute renal failure. Despite extreme therapeutic safety of this drug the clinician must be aware of this rare complication, which if detected early is completely reversible. ©

INTRODUCTION
Rifampicin is one of the key drugs that have helped to shorten the treatment duration in tuberculosis. Serious adverse reactions due to rifampicin are uncommon. Minor side effects like nausea and vomiting can be managed with symptomatic treatment. Rarely major adverse reactions endangering life such as thrombocytopenia¹ and acute renal failure²-⁴ may develop. Acute renal failure due to rifampicin therapy though uncommon has been described since 1971.⁵ It is usually reversible if detected early and treated appropriately.

The Tuberculosis Research Centre (TRC) of the Indian Council of Medical Research has conducted more than 30 controlled clinical trials for the treatment of pulmonary and extrapulmonary tuberculosis since 1956. From early 1970’s the TRC has been studying rifampicin-containing regimens for treating tuberculosis.⁶ More than 8000 patients with pulmonary or extra-pulmonary tuberculosis have been treated with rifampicin containing regimens (daily rifampicin regimens -2000,⁷,⁸ daily followed by intermittent rifampicin regimens -810⁹ and fully intermittent rifampicin - 5500⁹). Among these patients we are reporting three cases of acute renal failure, probably rifampicin-induced.

CASE REPORTS

Case I
A 25-year-old male weighing 39 kg presented in February 1997 with fever and cough for one month. He was normotensive and had crepitations in his right lung. Chest X-ray showed infiltration of the right upper and mid-zones. Four sputum smears were positive for tubercle bacilli by fluorescent microscopy, confirmed later by positive cultures. Hepatic and renal functions were normal.

The patient was treated with a daily rifampicin-containing regimen. Dosage of rifampicin was initially 450 mg and later increased to 600 mg because the patient gained weight. Though his compliance was not satisfactory, he responded well to treatment and had negative sputum smears and cultures at the end of treatment.

Five months after completing treatment he relapsed and anti-tuberculosis treatment was restarted with thrice-weekly isoniazid 600 mg, rifampicin 450 mg, ethambutol 1200 mg and pyrazinamide 1500 mg. After 20 days he complained of vomiting, anorexia, fever and oliguria. Blood urea was 173 mg/dl and serum creatinine 17.3 mg/dl. Ultrasound scan of the abdomen showed normal kidneys with increased cortical echoes.

A diagnosis of rifampicin-induced acute renal failure was made. He was treated with 3 sessions of peritoneal dialysis along with salt, protein and fluid restrictions with close monitoring of fluid intake and output. The patient refused to consent for renal biopsy. Renal function improved and in three weeks the blood urea was 45 mg/dl and serum creatinine 1.2 mg/dl. He was discharged from the hospital after another week with blood urea of 43 mg/dl and serum creatinine of 1mg/dl. The patient was successfully treated for tuberculosis with isoniazid 300 mg, ethambutol 800 mg, pyrazinamide 1000 mg daily from March 1998 for 12 months.

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Case II

A 25-year-old male weighing 46 kg was investigated for seizures, fever and vomiting in July 1987. Computerised Tomographic (CT) scan of the brain revealed a left parieto-temporal lesion suggestive of tuberculoma with gross edema. He was treated with 3 months of isoniazid 300 mg, rifampicin 450 mg, pyrazinamide 1000 mg daily followed by 6 months of isoniazid 600 mg and rifampicin 450 mg twice-weekly along with anticonvulsants (Eptoin, mazetol). He successfully completed treatment in April 1988 and the CT scan at the end of treatment showed a decrease in the size of the hyperdense lesion with no edema. A CT scan at the end of the 48th month was normal.

In October 1999, the patient presented with dry cough, fever, loss of weight and appetite of 3 weeks duration. Chest x-ray revealed parenchymal lesion of the upper zone of the left lung. Three sputum smears were positive for acid-fast bacilli and subsequently the cultures became positive. He was started on thrice-weekly treatment with isoniazid 600 mg, rifampicin 600 mg, ethambutol 1200 mg and pyrazinamide 1500 mg.

After 10 days the patient developed low back pain, anorexia and vomiting. He had renal angle tenderness. Blood urea was 77 mg/dl and serum creatinine 3.8 mg/dl. Renal biopsy showed diffuse mesangial proliferation with patchy interstitial inflammation. The basement membrane was not thickened. Tubules appeared unremarkable. The interstitium showed focal round cell infiltrates and blood vessels were mildly thickened. Acute renal failure was diagnosed and rifampicin was stopped; anti-TB treatment was continued with isoniazid 150 mg, ethambutol 800 mg and pyrazinamide 750 mg daily on the advice of the nephrologist. The renal failure was managed with peritoneal dialysis along with fluids, salt and protein restriction. Renal functions returned to normal after five days with blood urea of 25 mg/dl and serum creatinine of 1 mg/dl. The patient successfully completed anti-tuberculosis treatment with isoniazid 300 mg, ethambutol 800 mg, pyrazinamide 1500 mg followed by isoniazid 300 mg and ethambutol 800 mg daily for 13 months. He responded well to treatment with negative sputum smears and cultures.

Case III

A 25-year-old male weighing 46 kg presented in May 1996 with cough and fever for one month. He had taken irregular treatment for pulmonary tuberculosis elsewhere with a rifampicin-containing daily regimen for 5 months about a year before. He had crepitations and rhonchi in both lungs. Chest X-ray showed infiltration left mid-zone and right lower zone. Two sputum smears were positive for tubercle bacilli and subsequently the cultures became positive.
The histological feature of the biopsy in our patient was suggestive of immune complex deposition in the interstitium and blood vessels and is consistent with the predominant pattern observed by Muthukumar et al. in renal biopsy of 12 patients with rifampicin-induced acute renal failure. Fynn et al. reported a similar picture of interstitial edema in the renal biopsy of an oliguric patient after intermittent rifampicin therapy. According to De Vriese et al. acute tubular necrosis is the predominant pattern in renal biopsies during acute renal failure attributed to intermittent rifampicin therapy. Chan et al. explained that immune complex deposition with complement fixation leads to glomerular endothelial swelling which causes obstruction to the blood flow causing tubular ischemia.

Rifampicin therapy is a milestone in the treatment of pulmonary tuberculosis and is usually extremely safe. At TRC we have treated more than 8500 pulmonary and extrapulmonary tuberculosis patients with rifampicin-containing regimens in clinical trials. The regimens included daily and intermittent dosing. All patients were closely monitored for adverse drug events as part of the clinical trials protocols. We have not had a single case of renal failure in these patients during primary treatment. However during re-treatment with an intermittent rifampicin-containing regimen in 3 patients who had been previously treated with a daily rifampicin regimen we encountered acute renal failure. Our experience reinforces the fact of the extreme renal safety of this important drug, but still the physician must be aware of this rare life-threatening complication, which if detected early is completely reversible.

REFERENCES


Announcement

Echo and Color Doppler Centre, Sunder Lal Jain Hospital Complex, Ashok Vihar, Phase III, Delhi is again organizing the XIIth Comprehensive Course on Echocardiography from 2nd Oct. to 7th Oct. 2005. The course is absolutely based on American and European standards with emphasis on "Hand’s on Training programme". The Course is accredited by IMA Academy of Medical Specialities, Indian Academy of Echocardiography and Delhi Medical Council.

A limited number of participants with Hands on Training programme shall be enrolled as in previous courses. An accredited certificate shall be issued to each participant.

For further details contact: Dr. Rakesh Gupta, Organising Secretary Cum Course Director, Echo and Color Doppler Centre, Sunder Lal Jain Hospital, Ashok Vihar-III, Delhi -110052.
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